#18 Dec 11/20/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
	:	
Hallenbeck *et al.*	:	Art Unit: 1632
	:	
App. No. 09/373,938	:	Examiner: J. Woitach
	:	
Filed: August 13, 1999	:	Atty Docket: 4-30899P1
	:	
For: **Adenoviral Vectors Including DNA Sequences Encoding Angiogenic Inhibitors**	:	Confirmation No. 3124

DECLARATION OF PRIOR INVENTION UNDER 37 C.F.R. § 1.131

Box AF
Commissioner for Patents
Washington, D.C. 20231

Sir:

The inventors, Paul Hallenbeck and Cheauyun Theresa Chen, declare as follows:

1. We are the inventors of the invention described and claimed in U.S. Patent Application No. 09/373,938.

2. It is our understanding that claims 1, 2, 4-7, 11-17, 21-24, and 28-29 have been rejected under 35 U.S.C. § 102(a) as being anticipated by Leboulch *et al.* (WO 99/26480). It is also our understanding that claims 1-4, 7-10, 14, 18-21, and 25-33 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Leboulch *et al.* (WO 99/26480) taken with one or more other references. It is our understanding that Leboulch *et al.* (WO 99/26480) was published on June 3, 1999. Therefore, it is our understanding that Leboulch *et al.* (WO 99/26480) has an effective prior art date of June 3, 1999.

3. We make this Declaration in a traversal of these above stated rejections.

4. We conceived and reduced to practice the invention described and claimed in U.S. Patent Application No. 09/373,938 prior to June 3, 1999. In particular, prior to June 3, 1999, we conceived and reduced to practice an adenoviral vector comprising a DNA sequence encoding endostatin operatively linked to a promoter controlling expression of said DNA sequence.

5. As evidence of our prior invention, we attach hereto Exhibits A, B, and C. All dates in these Exhibits have been redacted. However, all redacted dates are prior to June 3, 1999.

6. Exhibit A is a draft of a Novartis Pharma Research internal study report, of which we are co-authors, entitled "Construction and Characterization of A Recombinant Adenoviral Vector Encoding Secreted Murine Endostatin *in vitro*." This report describes the preparation of the replication deficient recombinant adenoviral vector, Av3mEndo, encoding murine endostatin in a secreted form. This report further describes the expression and secretion of biologically active murine endostatin in Av3mEndo-transduced Hep3B (human hepatoma) and S8 (human lung carcinoma derived) cells. This report formed the basis for Example 1 of the instant application's specification.

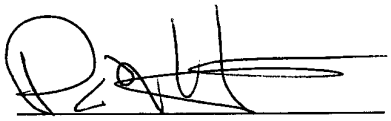
7. Exhibit B is a draft of a Novartis Pharma Research internal study report, of which we are co-authors, entitled "Characterization of Av3mEndo in Animal Tumor Models." This report describes the *in vivo* efficacy study of Av3mEndo in various animal tumor models, naturally occurring colon liver metastasis model, B16F10 seeded lung metastasis model, and B16F10 subcutaneous model. This report further sets forth that Av3mEndo administration demonstrated systemic secretion of endostatin at a much higher levels than the endogenous endostatin of the controls. In the colon liver metastasis model, systemic secretion of endostatin rendered extended survival in colon liver metastasis bearing mice. In the B16F10 lung metastasis model, Av3mEndo demonstrated an additional anti-metastasis effect over the control. This report formed the basis for Example 2 of the instant application's specification.

8. Exhibit C consists of copies of laboratory notebook pages that show the preparation of Av3bmhendlx, a recombinant adenoviral vector encoding human endostatin fused to the BM40 basement protein leader sequence. These notebook pages also show the expression and secretion

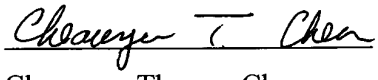
of human endostatin in Av3bmhendlx-transduced S8 cells. These notebook pages formed the basis for Example 4 of the instant application's specification. The experiments shown in notebook numbers 1003 and 1060 were performed by Sandrina Phipps under Cheauyun Theresa Chen's supervision and direction and were witnessed by Lori M. Clarke. The experiments shown in notebook number 1127 were performed by Qin Li under Cheauyun Theresa Chen's supervision and direction and were witnessed by Ke Wen. The experiments shown in notebook number 1080 were performed by Cheauyun Theresa Chen and were witnessed by Marina O'Reilly.

9. All statements made herein of our own knowledge are true and all statements made on information and belief are believed to be true. Further, these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Subscribed to on the following date:

Nov 21, 2002 

Paul Hallenbeck

Nov. 21, 2002 

Cheauyun Theresa Chen